Chemistry of Heterocyclic Compounds, Vol. 34, No. 3, 1998

INTERMEDIATES IN THE REACTION OF *o*-PHENYLENE-DIAMINE WITH CARBONYL COMPOUNDS AND THEIR SUBSEQUENT CONVERSIONS

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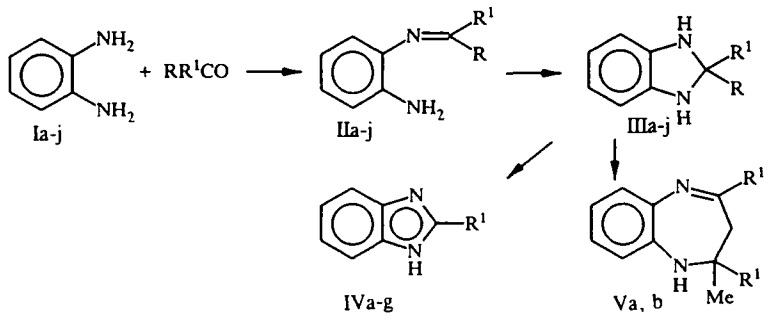
The reaction of o-*phenylenediamine with aldehydes and ketones has been studied using PMR spectroscopy. It has been established that the reaction begins with the formation of monoimines (isolated in condensations with aromatic aldehydes) which are cyclized to the corresponding benzimidazolines. The latter are converted in the reactions involving aldehydes and pinacolone into 2-substituted benzimidazoles, but with acetone and acetophenone give 2,3-dihydro-1H-benzo[b]-1,4-diazepine derivatives.*

The reaction of *o*-phenylenediamines with aldehydes and ketones, known since 1879 [1], is one of the universal methods of synthesizing benzimidazole derivatives [1-4]. If enolizable ketones are used in the condensation it becomes a convenient method of obtaining 2,3-dihydro-1H-benzo[*b*]-1,4-diazepines [5, 6]. The reaction has been applied to the synthesis of the corresponding bisimines in individual cases [7, 8]. Products of the reaction of aldehydes with o-phenylenediamine are used preparatively without isolation for the reduction of electron-deficient multiple bonds [9, 10].

It is assumed that the formation of the corresponding monoimine is the basis of these conversions. However it was isolated only in the reaction with certain aromatic aldehydes containing a hydroxyl group [8] and also with benzaldehyde [11], though the reaction conditions and characteristics were not given in the latter. In some studies [9, 10] the monoimines were characterized spectrally without isolation from the reaction mixture. Attempts have also been made to follow the course of the interaction of *o*-phenylenediamine with hydroxy compounds [6], but they gave no positive result. Thus the view which has been assembled [3], that the synthesis of benzimidazoles is effected through the stage of forming a monoimine, its subsequent cyclization into a benzimidazoline with dehydrogenation (dealkylation) of the latter, has not been confirmed experimentally.

The present investigation was undertaken with the aim of clarifying this problem. We also selected reaction conditions in order to avoid the formation of bisimines and the subsequent complex conversions connected with this [11]. A two-fold excess of phenylenediamine in DMSO-D_6 was used, to which the appropriate carbonyl compound was added. The course of the condensation was followed by PMR spectroscopy.



I—IV a R = H, R^1 = Me; b R = H, R^1 = Et; c R = H, R^1 = Pr; d R = H, R^1 = *i*-Pr; e R = H, R^1 = Ph; f R = H, R^1 = 4-$MeOC_6H_4$; g R = H, R^1 = $MeOCOC_6H_4$; h R = R^1 = Me; i R = Me, R^1 = *t*-Bu; j R = Me, R^1 = Ph; V a R^1 = Me, b R^1 = Ph

Academy of Military Medicine, Saint Petersburg 194175, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 363-367, March, 1998. Original article submitted July 15, 1997.

0009-3122/98/3403-0329$20.00

TABLE 1. PMR Spectra of Compounds (IIa-g, j) and (IIIa-j) in DMSO-D_6

Compound	PMR Spectrum, ppm (coupling constant, J, Hz)			
	R	R^1	H_{arom}	NH
IIa	8.04 (1H, q, 6.0)	2.10 (3H, d, 6.0)	6,45...7,12 (4H, m)	4.72 (2H, br. s)
IIb	8.07 (1H, t, 6.0)	1.25 (3H, t, 6.0); 2.41-2.55 (2H, m)	6,34...7,09 (4H, m)	4,84 (2H, br. s)
IIc	8.02 (1H, t, 6.5)	10.3 (3H, t, 6.0); 1.62-1.76 (2H, m); 2.42-2.57 (2H, m)	6,40...7,02 (4H, m)	4.87 (2H, br. s)
IId	8.00 (1H, t, 6.5)	1.23 (6H, d, 6.0); 2.55-2.71 (1H, m)	6,43...7,17 (4H, m)	5.11 (2H, br. s)
IIe	8.44 (1H, s)	6.27-7.93 (5H, m)	6,27...7,93 (4H, m)	5.02 (2H, br. s)
IIf	8.32 (1H, s)	3.51 (3H, s); 6.25-7.81 (4H, m)	6,25...7,81 (4H, m)	5.08 (2H, br. s)
IIg	8.57 (1H, s)	3.70 (3H, s); 6.28-7.98 (4H, m)	6,28...7,98 (4H, m)	5.12 (2H, br. s)
IIj	2.39 (3H, s)	6.51-8.03 (5H, m)	6,51...8,05 (5H, m)	4.59 (2H, br. s)
IIIa	5.03 (1H, q, 6.0)	1.08 (3H, d, 6.0)	6,45...6,80 (4H, m)	4.73 (2H, br. s)
IIIb	5.17 (1H, t, 6.0)	1,01 (3H, t, 6.0); 1.51-2.65 (2H, m)	6,43...6,77 (4H, m)	4.67 (2H, br. s)
IIIc	5.11 (1H, t, 6.5)	0.99 (3H, t, 6.0); 1.52-1.66 (4H, m)	6,44...6,77 (4H, m)	4.64 (2H, br. s)
IIId	5.06 (1H, t, 6.5)	1.03 (6H, d, 6.0); 1.61-1.81 (1H, m)	6,44...6,85 (4H, m)	4.86 (2H, br. s)
IIIe	5.60 (1H, s)	6.27-7.93 (5H, m)	6,27...7,93 (4H, m)	4.41 (2H, br. s)
IIIf	5.77 (1H, s)	3.77 (3H, s); 6.55-7.86 (4H, m)	6,55...7,86 (4H, m)	4.29 (2H, br. s)
IIIg	6.04 (1H, s)	3.65 (3H, s); 6.35-8.10 (4H, m)	6,35...8,10 (4H, m)	4.59 (2H, br. s)
IIIh	1.43 (3H, s)	1.43 (3H, s)	6,44...6,83 (4H, m)	4.66 (2H, br. s)
IIIi	1.79 (3H, s)	6.51-8.05 (5H, m)	6,51...8,05 (4H, m)	5.80 (2H, br. s)
IIIj	1.33 (3H, s)	1.00 (9H, s)	6,59...6,91 (4H, m)	5.95 (2H, s)

TABLE 2. Characteristics of Benzimidazoles (IVa-g)

Compound	mp, °C	PMR Spectrum in DMSO-D_6, ppm (coupling constant, J, Hz)		
		R^1	H_{arom}	NH
IVa	177...178	2.74 (3H, s)	7.21-7.69 (4H, m)	4.55 (1H, br. s)
IVb	175...176	1.45 (3H, t, 6.0); 3.01 (2H, q)	7.20-7.61 (4H, m)	4.61 (1H, br. s)
IVc	150...151	1.13 (3H, t, 6.0); 1.82-2.01 (2H, m); 2.86-3.09 (2H, t, 6.0)	7.22-7.70 (4H, m)	4.54 (1H, br. s)
IVd	226...228	1.54 (6H, d, 6.0); 1.82-2.01 (1H, m)	7.26-7.74 (4H, m)	4.60 (1H, br. s)
IVe	287...290	6.47-7.16 (5H, m)	7.70-8.37 (4H, m)	4.53 (1H, br. s)
IVf	229...231	3.97 (3H, s); 6.85-7.29 (4H, m)	6.85-7.29 (4H, m)	4.67 (1H, br. s)
IVg	194...196	3.95 (3H, s); 6.93-8.05 (4H, m)	6.93-8.05 (4H, m)	4.58 (1H, br. s)

A large difference in the reactivity of aldehydes and ketones was observed under these conditions. Ketones do not react in this case. The behavior of aliphatic and aromatic aldehydes was different. An aromatic aldehyde reacted instantaneously but the consumption of a saturated aldehyde may be followed with time. The unbranched aldehydes (Ia-c) were consumed during 5-10 min but isobutyraldehyde (Id) disappeared completely after approximately 30 min. In all cases the monoimines (IIa-g) were formed quantitatively.

Their structures were proved unequivocally by the presence of a signal for the resonance of the azomethine proton of appropriate intensity at 8.0-8.5 ppm and by other PMR spectral data (Table 1).

The derivatives of aromatic aldehydes (IIe-g) were stable irrespective of the electronic properties of the substituent in the para position of the aromatic ring and it was possible to isolate them in the pure state from a condensation at a 1:1 reactant ratio (see Experimental).

Solutions of monoimines (IIa-d) behaved in a different way. They were quantitatively converted in the course of several hours into the corresponding benzimidazolines (IIIa-d) (Table 1) which was confirmed by the replacement of the azomethine proton signal in the PMR spectrum by a signal for the 2-H proton at 5.0-6.0 ppm. The same conversion occurs instantaneously if a catalytic amount of trifluoroacetic acid is added to the solution.

Cyclization of monoimine (II) into benzimidazoline (III) by the catalytic action of CF_3COOH was also observed in solutions of the aromatic monoimines (IIe-g) (see Table 1). However this occurs during several days and is accompanied by the gradual accumulation of dehydrogenation products, viz. the benzimidazoles (IVe-g). These were isolated preparatively and characterized (Table 2) at the end of the reaction (which requires several days). The benzimidazolines (IIIe-g) are therefore unstable and both monoimine and benzimidazole are contained in reaction mixtures.

The benzimidazolines (IIIa-d) were not isolated and obtained quantitatively since directly after their formation in solution it was possible to detect the presence of the corresponding benzimidazoles (IVa-d) (Table 2). These became the sole products after several days irrespective of whether the reaction was carried out with the catalytic action of acid or in its absence.

The difference in the stability of the saturated and aromatic monoimines may be explained by stabilization of the latter by π,π,π-conjugation.

The ketones (Ih-j) (acetone, acetophenone, pinacolone) also reacted with o-phenylenediamine with CF_3COOH catalysis, however their behavior was different from that of the aldehydes and differed among themselves.

Reaction with acetone (Ih) occurred instantaneously and the sole product was the corresponding benzimidazoline (IIIh). The high field singlet signal of the methyl groups (1.43 ppm, Table 1) at the sp^3 $C_{(2)}$ carbon atom proves the structure of this substance unequivocally. However it was not isolated since even after a few minutes it was possible to detect the presence of the corresponding 2,2,4-trimethyl-2,3-dihydro-1H-benzo[*b*]-1,4-diazepine (Va) in the reaction mixture. After approximately one week the benzodiazepine became the sole reaction product and was isolated and characterized (see Experimental).

The reaction of acetophenone (Ij) with *o*-phenylenediamine proceeded slowly. Only after several days was it completely consumed. The resulting monoimine (IIj) (Table 1) immediately began to undergo cyclization into benzimidazoline (IIIj) (Table 1), which was gradually transformed into the sole isolated reaction product 2-methyl-2,4-diphenyl-2,3-dihydro-1H-benzo[*b*]-1,4-diazepine (Vb) (see Experimental). All three compounds (II), (III), and (V) were present in the reaction mixture from the beginning of the reaction as in the case of the reaction of *o*-phenylenediamine with aromatic aldehydes in the presence of trifluoroacetic acid.

The difference in behavior of acetone and acetophenone must be due both to the lower reactivity of the latter on condensation with the amine due to steric reasons [which slows the formation of monoimine (IIj)] and to the stabilization of monoimine (IIj) as a result of π,π,π-conjugation [which inhibits the cyclization to benzimidazoline (IIIj)].

The formation of benzodiazepines (V) and not benzimidazoles (IV) in the reaction with ketones is a result of the fact that the dealkylation necessary for the conversion of benzimidazoline to benzimidazole occurs under more forcing conditions than the dehydrogenation in the case of aldehyde derivatives [3]. On the other hand there are none of the usual difficulties for the conversion into benzodiazepines which may be explained in several ways [6]. The simplest of them is the possible fission of the benzimidazoline ring with transfer of it into monoimine, hydrolysis of the monoimine to the initial components, subsequent aldolization of the ketone and condensation of the aldolization product with *o*-phenylenediamine.

It is proposed that in the reaction with ketones destabilization of the monoimine on the one hand and steric hindrance towards aldolization on the other may lead to the preparation of stable benzimidazolines without substituents on the nitrogen atoms, concerning which there is no information. This might have been expected in the reaction with pinacolone. As in the condensation with acetophenone this reaction proceeds slowly even on catalysis with trifluoroacetic acid. However, as in the reaction with acetone, benzimidazoline (IIIi) (Table 1) is formed but is gradually dealkylated into 2-methylbenzimidazole (IVa) (Table 2). After a week only this product and unreacted pinacolone (Ii) were detected in the reaction mixture.

By selecting reaction conditions and by varying the structure of the carbonyl component it has therefore been possible to observe the sequential course of the reaction in stages of monoimine → benzimidazoline → final product (benzimidazole or 2,3-dihydro-1H-benzo[*b*]-1,4-diazepine). It turned out possible to obtain the corresponding stable intermediates and 2-(1-arylmethylideneamine)phenylamines (by reaction with aromatic aldehydes). On the whole this reaction may be considered as a method of synthesizing benzimidazoles from aldehydes and 2,3-dihydro-1H-benzo[*b*]-1,4-diazepines

from enolizable ketones. If monoimines are used (more precisely, benzimidazolines isomeric with them) as sources of hydrogenation of the unsaturated compounds two variants of carrying out this reaction may be recommended. One is the use of 2-(1-arylmethylideneamino)-phenyl-amines prepared previously and stable on storage and the other is their generation *in situ* by the reaction of alkanals with an excess of *o*-phenylenediamine.

EXPERIMENTAL

The PMR spectra were recorded on a Tesla BS 497 (100 MHz) instrument.

Condensation of *o*-Phenylenediamine with Carbonyl Compounds. The appropriate carbonyl compound (0.5 mmole) was added to a solution of *o*-phenylenediamine (0.108 g, 1 mmole) in DMSO-D_6 (1 ml). The reaction was followed using PMR spectral data. In the case of carbonyl compounds (Ia-d) and (Ih-j) the corresponding unstable monoimines and benzimidazolines were formed as intermediates and in the course of time were isomerized into benzimidazoles (IV) or benzodiazepines (V) (see Discussion). These were identified from PMR spectral data (Table 2) and by alternate synthesis. In the case of benzaldehyde (Ie), 4-methoxybenzaldehyde (If), and 4-methoxycarbonylbenzaldehyde (Ig) the monoimines were stable and were isolated preparatively.

2-Benzylideneaminoaniline (IIe). A solution of benzaldehyde (1.06 g, 10 mmole) in methanol (10 ml) was added dropwise during 30 min to a solution of *o*-phenylenediamine (1.08 g, 10 mmole) in methanol (10 ml). Water (50 ml) was added to the reaction mixture, the precipitated crystals were filtered off, and dried in a desiccator over P_2O_5 for 2 days. Yield was 1.71 g (87%) of mp 63-64°C. Found, %: C 79.56; H 6.16; N 14.27. $C_{13}H_{12}N_2$. Calculated, %: C 79.67; H 6.11; N 14.35.

2-(4-Methoxyphenylmethyleneamino)aniline (IIf). A solution of 4-methoxybenzaldehyde (1.36 g, 10 mmole) in methanol (10 ml) was added dropwise during 30 min to a solution of *o*-phenylenediamine (1.08 g, 10 mmole) in methanol (10 ml). The mixture was stored at room temperature for 30 min and then cooled to −5°C. The precipitated crystals were filtered off and dried in a disiccator over P_2O_5 for 2 days. Yield was 1.56 g (69%) of mp 98-99°C. Found, %: C 74.31; H 6.24; N 12.38. $C_{14}H_{14}N_2O$. Calculated, %: C 74.22; H 6.15; N 12.45.

2-(4-Methoxycarbonylphenylmethyleneamino)aniline (IIg) was obtained analogously to compound (IIf). Yield was 2.34 g (92%) of mp 131-132°C. Found, %: C 70.85; H 5.55; N 11.02. $C_{15}H_{14}N_2O_2$. Calculated, %: C 70.77; H 5.50; N 11.15.

The known benzimidazoles (IV) were obtained by the reaction of *o*-phenylenediamine with the appropriate carbonyl compounds by the procedure of [12]. The constants of compounds (IVa-f) (Table 2) agreed with literature data.

2-(4-Methoxycarbonylphenyl)benzimidazole (IVq) was obtained analogously from o-phenylenediamine and 4-methoxycarbonylbenzaldehyde. Yield was 72% of mp 194-196°C. Found, %: C 71.42; H 4.79; N 11.10. $C_{15}H_{12}N_2O_2$. Calculated, %: C 71.57; H 4.71; N 11.22.

2,2,4-Trimethyl-2,3-dihydro-1H-benzo[*b*]-1,4-diazepine (Va). A solution of *o*-phenylenediamine (1.08 g, 10 mmole) and acetone (1.16 g, 20 mmole) in methanol (15 ml) was boiled under reflux in the presence of a catalytic quantity of trifluoroacetic acid for 1 h. The solvent was evaporated in vacuum and the residue recrystallized from heptane. Yield was 1.53 g (81%) of mp 104°C. PMR spectrum (DMSO-D_6): 1.27 (3H, s, CH_3); 1.33 (3H, s, CH_3); 2.25 (2H, br.s, CH_2); 2.30 (3H, s, CH_3); 4.25 (1H, s, NH); 6.50-6.95 ppm (4H, m, H_{arom}).

Compound (Vb) was prepared analogously. Yield was 2.32 g (82%) of mp 124-125°C. PMR spectrum (DMSO-D_6): 1.69 (3H, s, CH_3); 2.91, 3.29 (2H, J_{AB} = 13.0 Hz, CH_2); 4.85 (1H, s, NH); 6.70-7.75 ppm (14H, m, H_{arom}). Compounds (Va, b) were identical to samples obtained by the procedure of [13].

The authors are grateful to the Russian Fund for Fundamental Investigations (RFFI) for financing the investigation into the chemistry of diamines (Project Code No. 97-03-33028a).

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